Symmetry of Hydrogen Bonds in Two Enols in Solution

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Abstract: The enols of 4-cyano-2,2,6,6-tetramethyl-3,5-heptanedione and of nitromalonamide were prepared as statistical mixtures of $^{18}O_n$ (n = 0,1,2) isotopologues. The symmetries of their hydrogen bonds were probed by isotopic perturbation of their ^{13}CO NMR signals. The former mixture shows a total of four signals, due to both intrinsic and perturbation isotope shifts. Therefore that enol is a mixture of tautomers with an asymmetric hydrogen bond. In contrast, the mixture of isotopologues of nitromalonamide enol shows only two signals, due to an intrinsic isotope shift. Therefore this is the first case, to be compared with FHF^- anion, of a neutral species with a single symmetric structure in solution, and with a centered hydrogen.

Introduction

Hydrogen bonding (H-bonding) is a fundamental aspect of chemical structure and reactivity.[1] H-bonds contribute to the shape and function of substances such as water, proteins, and DNA. The principles of H-bonding are so basic that they are taught in all elementary chemistry courses, yet so complex that they continue to be actively studied.[2-4] In recent years H-bonds have been exploited for enhancing cobalt-catalyzed CO_2 reduction,[5] and they have been recognized as promoting enantioselective Michael additions catalyzed by a Co(III) complex.[6]

The question addressed here is whether the potential energy describing a hydrogen bond A···H···B is single-well or double-well, as illustrated in Fig. 1. Most often, as in water, proteins, and nucleic acids, the double-well potential is asymmetric, with one well deeper than the other (Fig. 1a). In this case the hydrogen is attached by a single bond to atom A and H-bonded to B. If the two wells are of equal energy (Fig. 1b), the hydrogen can jump or tunnel from A to B and back. Finally, as the distance between A and B decreases, the barrier between the wells disappears, resulting in a single-well potential (Fig. 1c). This seems to occur when the A-B distance decreases to 2.4-2.5 Å.

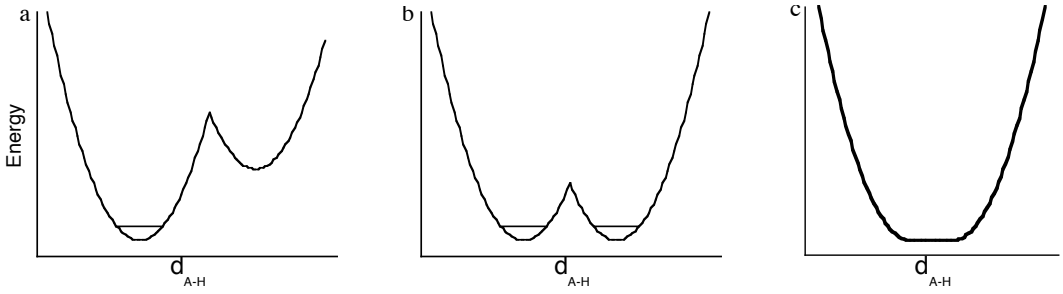


Figure 1. Potential energy for H motion in A···H···B hydrogen bond. (a) Asymmetric double well. (b) Symmetric double well. (c) Single well.

Single-well or low-barrier H-bonds are thought to be unusually strong.[7] However, it is difficult to distinguish experimentally between a centered proton in a single-well potential and a proton undergoing a static or dynamic disorder in a double-well potential. The designation "short", "strong", or "low-barrier" then depends on the criterion used for characterization.

Such H-bonds have attracted great interest for their possible role in stabilizing intermediates or transition states in enzyme-catalyzed reaction.[8] Nevertheless, this interpretation

is controversial,[9] and a recent article addresses critically the relationships among bond length, pK_a difference, and stability.[10] Regardless of any relevance to enzymes, the question of H-bond structure is a fundamental one, worthy of addressing in its own right.

We have been addressing this topic by seeking symmetric H-bonds in solution.[11] Nuclear magnetic resonance (NMR) methods are powerful in this regard.[12] Our approach has been to use the method of isotopic perturbation,[13] as developed by Saunders and coworkers,[14] in order to distinguish a single tautomer in a single-well potential from a mixture of tautomers in a double-well potential. This depends on measuring the isotope shift ${}^{n}\Delta_X$, which is the change of the NMR chemical shift δ of a reporter nucleus X due to isotopic substitution *n* bonds away (eq 1). There are two contributions to the isotope shift, an intrinsic isotope shift Δ_0 and a perturbation shift Δ_p induced by isotopic perturbation of an equilibrium (eq 2). The example of mono-deuterium-substituted 3-hydroxy-2-phenylpropenal (phenylmalondialdehyde enol, HOCH=CPh-CH=O) is illustrative.[15] Because this is a mixture of two tautomers, depending on whether the D is on the enol or aldehyde carbon, the vibrational frequencies and zero-point energies of the two possible tautomers are different. The average NMR chemical shift is then weighted toward that of the more stable tautomer, leading to a nonzero Δ_p, as given in eq 3, where δ_{COH} or δ_{CO^-} is the ^{13}C chemical shift of a carbon attached to OH or O^- and *K* is equal to K_a^{16}/K_a^{18}, the ratio of the acidity constants of ^{16}O and ^{18}O acids. In contrast, there is no perturbation for unlabeled or doubly labeled enol, comparison with which serves to evaluate Δ_0. In this way 3-hydroxy-2-phenylpropenal was shown to be a mixture of tautomers, with an asymmetric H-bond.

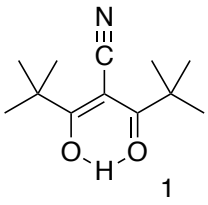
$$ {}^{n}\Delta_X = \delta_{heavy} - \delta_{light} \qquad (1) $$

$$ \Delta_{obs} = \Delta_0 + \Delta_p \qquad (2) $$

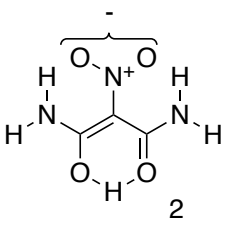
$$\Delta_p = (\delta_{COH} - \delta_{CO^-})(K\text{-}1)/2(K\text{+}1) \quad (3)$$

Moreover, all the H-bonds that we have investigated are asymmetric in solution, especially in the monoanions of dicarboxylic acids and other acid-base pairs, some of which are found to be symmetric in crystals.[16,17] Our interpretation is that the disorder of solvation, as well as the unlikelihood of identical solvation of A and B, renders the H-bonds instantaneously asymmetric.[18,19] The asymmetry was therefore ascribed to the presence of "solvatomers", or isomers that differ in solvation.[20] Even the classic case of the bifluoride ion FHF^- can be desymmetrized owing to fluctuations of the positions of solvent molecules.[21] Moreover, we concluded that there is no stabilization associated with symmetric, short, or low-barrier H-bonds. If they were so stable, the local solvation environment should not be capable of disrupting their symmetry. It must be acknowledged that the isotope shifts that we detect have been reinterpreted as arising from the trajectory of anharmonic H motion,[22] although we have countered with the observation that the isotope shifts are larger at lower temperature, consistent with isotopic perturbation of an equilibrium.[23]

Bulky substituents force the two oxygens closer together and favor a single-well potential,[24] as do electron-withdrawing substituents at the central carbon.[25] Therefore we have undertaken to investigate the symmetry of the H-bonds in two enols, 4-cyano-2,2,6,6-tetramethyl-3,5-heptanedione enol (**1**) and nitromalonamide enol (**2**). It should be noted that in solution the latter happens to be in equilibrium with its diketone (diamide) tautomer (**3**) that lacks the H-bond.



1



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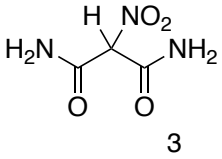


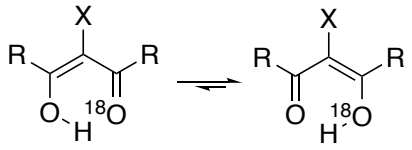
3

Both **1** and **2** are prominent candidates for a centered H. The O-O distance in **1**, measured by X-ray diffraction in the crystal, is an unusually short 2.393 Å.[26] Moreover, X-ray crystallography shows an almost perfectly C_{2v}-symmetric structure, with C-O bond lengths of 1.273 and 1.274 Å and C-C bond lengths of 1.430 and 1.432 Å. The two-fold symmetry is not imposed by the lattice. However, according to neutron-scattering measurements, the H is nearly centered between the two oxygens but in a low-barrier double-minimum potential.

For **2** the O-O distance is 2.391 Å.[27] According to neutron-diffraction studies the H is located asymmetrically between the two oxygen atoms in the otherwise quite symmetrical molecule, with O-H distances of 1.14 Å and 1.31 Å, but in a single-well potential. The barrier to proton transfer was calculated to be only 0.15 kcal/mol at the MP2/cc-pVTZ level or 0.3 kcal/mol at the B3LYP/cc-pVTZ level. Other calculations obtained barriers of 0.43 and 0.33 kcal/mol,[28,29] and these may be below the zero-point energy for H motion. In view of the uncertainties regarding the symmetry and the barrier, it was concluded that "a remaining goal is the identification of a substituted malonamide with no barrier at all, i.e., a C_{2v} equilibrium geometry". Indeed, still another computational study concluded that the H is highly mobile between the two oxygens and is not in a double-well potential or in a tautomeric equilibrium.[30] In summary, it must be recognized that the barrier heights in **1** and **2** are quite uncertain.

We therefore investigate both **1** and **2** by the method of isotopic perturbation. If either of these is a mixture of two tautomers that differ depending on which O bears the H, the equilibrium between those two tautomers will be perturbed by replacing one ^{16}O by ^{18}O. Because the stretching frequency and zero-point energy are greater for ^{16}O-H than for ^{18}O-H, the equilibrium will favor the tautomer with H on the ^{18}O, as suggested in Scheme 1. Indeed, this is responsible for the observation that ^{18}O-substituted carboxylic acids are weaker than ^{16}O-

substituted acids.[31] The perturbation of the tautomeric equilibrium can then be sensed by a difference in ^{13}C chemical shifts between the two carbonyl carbons.



Scheme 1. Perturbation by ^{18}O of a postulated tautomeric equilibrium in **1** (R = t-Butyl, X = CN) and **2** (R = NH_2, X=NO_2).

Rather than attempting the challenging synthesis of specifically monolabeled **1**-^{18}O and **2**-^{18}O, we have undertaken to synthesize statistical mixtures of $^{18}O_n$ isotopologues (n = 0,1,2), where isotopologues are species that differ only in the number of isotopic substitutions. Incorporation of ^{18}O into 2,2,6,6-tetramethyl-3,5-heptanedione by exchange with $H_2{}^{18}O$ under acid catalysis, followed by cyanation to form **1**, is straightforward. Incorporation of ^{18}O into **2** by exchange of malonamide with $H_2{}^{18}O$ under base catalysis, followed by nitration, requires careful control because of hydrolysis competing with exchange. The rate of malonamide hydrolysis had been measured,[32] and the ratio of the rate of hydrolysis to the rate of ^{18}O exchange in the model amide benzamide is 0.21 at 109 ºC,[33] so that the hydrolysis could be carried out to ~20% completion in order to obtain extensive exchange.

We now report that **1** is a mixture of tautomers, whereas **2** is a single, symmetric species. This is the first example, other than the classic FHF^-, of a symmetric H-bond in solution.

Results

At either 21.6 ºC or -20.0 ºC the ^{13}C NMR spectrum of enol **1**-$^{18}O_n$ isotopologues (n = 0,1,2) in $CDCl_3$ shows four signals in the carbonyl region near 210 ppm. Figure 2 shows those four signals, designated as $A_{1\text{-}4}$ in order from most deshielded (downfield) to least, at 21.6 ºC.

Figure S1 shows those four signals at -20.0 ºC. Table 1 lists their chemical shifts at both 21.6 ºC and -20.0 ºC.

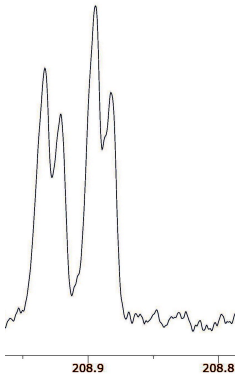


Figure 2. Carbonyl signals near 210 ppm in the ^{13}C NMR spectrum of enol **1**-$^{18}O_n$ isotopologues (n = 0,1,2) at 21.6 º C in $CDCl_3$.

Table 1. ^{13}C chemical shifts (ppm) for carbonyl signals of enol **1**-$^{18}O_n$ isotopologues (n = 0,1,2) in $CDCl_3$.

Temperature	Signal A_1	Signal A_2	Signal A_3	Signal A_4
21.6 ˚C	208.9204	208.9083	208.8816	208.8695
-20.0 ˚C	209.1264	209.1118	209.0864	209.0717

The intensities of the signals in Fig. 2 are in the order $A_3 > A_1 \geq A_4 > A_2$. From the 1.3:1 ratio of ^{18}O to ^{16}O derived from the mass-spectrometric populations in Table S1, A_3, the most intense signal, can be assigned to the two carbons of **1**-$^{18}O_2$ and A_2, the least intense, to the two carbons of **1**-$^{16}O_2$. The other two signals, A_1 and A_4, can be assigned to the two carbons of **1**-$^{18}O_1$. Which of those is the C-^{16}O and which is the C-^{18}O is indeterminate, but for definiteness (and because it does not affect the conclusion but only the magnitude of the perturbation shift)

we assign A_1 to the C-^{16}O and A_4 to the C-^{18}O. In support of these assignments, only signal A_2 is enhanced on adding authentic **1**-$^{16}O_2$.

The ^{13}C NMR spectrum of enol **2**-$^{18}O_n$ isotopologues (n = 0,1,2) in DMSO-d_6 shows two carbonyl signals near 170 ppm. Figure 3 shows those signals, designated as A_1 and A_2 in order from more deshielded (downfield) to less, at 21.6 ºC. Figure S2 shows two additional carbonyl signals, designated as A_1' and A_2', near 162 ppm, due to the diketone **3**-$^{18}O_n$ isotopologues (n = 0,1,2). All these signals, slightly less well resolved but with the same splittings, are also seen at -20 ºC in 1:1 CD_3CN-DMSO-d_6 (not shown). The intensities of these carbonyl signals are in the order $A_1 > A_2$, and they match the 1:1.4 ratio of ^{18}O to ^{16}O derived from the mass-spectrometric populations in Table S2. Therefore, in both cases, A_1, the more intense signal, can be assigned to the carbon attached to ^{16}O and A_2, the less intense, to the carbon attached to ^{18}O. Table 2 lists the chemical shifts of those carbonyl signals, in order from more deshielded (downfield) to less.

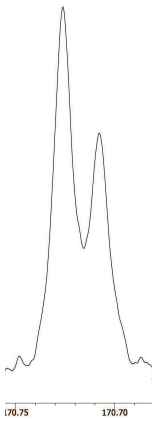


Figure 3. Carbonyl signals near 170 ppm in the ^{13}C NMR spectrum of enol **2**-$^{18}O_n$ isotopologues (n = 0,1,2) at 21.6 ºC in DMSO-d_6.

Table 2. ^{13}C chemical shifts (ppm) for carbonyl signals of enol **2**-$^{18}O_n$ and diketone **3**-$^{18}O_n$ isotopologues (n = 0,1,2) at 21.6 ºC in DMSO-d_6.

	Signal A_1	Signal A_2
Enol	170.7160	170.6974
Diketo	161.9589	161.9274

Discussion

Table 3 lists the separations between successive signals of enol **1**-$^{18}O_n$ in Table 1. Because A_2 and A_3 are due to **1**-$^{16}O_2$ and **1**-$^{18}O_2$, respectively, the separation between them cannot have any contribution from isotopic perturbation of an equilibrium and must be an intrinsic isotope shift Δ_0. The other two separations, A_1 - A_2 or $A_3 - A_4$, are due to the isotope shift on a C-^{16}O or C-^{18}O due to perturbation of an equilibrium by a remote ^{18}O. These assignments as intrinsic isotope shifts Δ_0 and perturbation isotope shifts Δ_p are included in Table 3. In support of these assignments, the intrinsic isotope shifts are temperature-independent, within experimental error, and the two values for the perturbation shifts at each temperature are also the same, within experimental error. Noteworthy is the result that the perturbation shift is larger at the lower temperature.

Table 3. Chemical-shift differences (ppb) for carbonyl signals of enol **1**-$^{18}O_n$ isotopologues (n = 0,1,2) and assignments as intrinsic or perturbation ^{18}O-induced isotope shifts.

Difference	21.6 ˚C	-20.0 ˚C	Type
A_1 - A_2	12.1	14.7	Δ_p
$A_2 - A_3$	26.7	25.4	Δ_0
$A_3 - A_4$	12.1	14.6	Δ_p

The temperature dependence of Δ_p shows that the non-zero value of Δ_p is unlikely to result from the anharmonicity of hydrogen-atom motion, as the effect of anharmonicity should be larger at higher temperature. In contrast, the larger perturbation shift at the lower temperature is consistent with an isotope effect on an equilibrium between tautomers. Because that isotope effect, as in eq 3, is due to differences in zero-point energies or enthalpies, it then follows that $d(\ln K)d(1/T)$ is greater than 0. Therefore, we conclude that the hydrogen-bond in **1** is asymmetric, with a double-well potential.

Table 4 lists the separations between successive signals of enol **2**-$^{18}O_n$ in Table 2. Approximately the same separations are seen at -20 ºC in 1:1 CD_3CN-DMSO-d_6 (not shown). Because there are only two signals, not the four for **1**-$^{18}O_n$, there is no detectable isotope shift due to perturbation of an equilibrium, even though the parameters in eq 3 are the same for **2** as for **1** so that a perturbation shift of 12 ppb would have been resolved. Therefore, they must be assigned as intrinsic isotope shifts, as also indicated in Table 4. In support, the intrinsic isotope shift is greater for the diketone tautomer **3** than for the enol **2** because there is more C-O double-bond character in the diketone. Moreover, the intrinsic isotope shift in this enol is lower than that in enol **1**, consistent with a reduction of its C-O double-bond character by delocalization of the amide nitrogen's lone pair. Therefore, we conclude that the H-bond in enol **2** is symmetric, with a centered hydrogen.

Table 4. Chemical-shift differences (ppb) for carbonyl signals of enol **2**-$^{18}O_n$ and diketone **3**-$^{18}O_n$ isotopologues (n = 0,1,2) and assignments as intrinsic ^{18}O-induced isotope shifts.

	Difference	Type
$A_1 - A_2$ (**2**)	18.6	Δ_0

$A_1' - A_2'$ (**3**)	31.5	Δ_0

This conclusion is not inconsistent with the neutron-diffraction result that the O-H distances in **2** are 1.14 Å and 1.31 Å, because although the overall molecule is quite symmetrical, only one of its enolic oxygens is intermolecularly H-bonded to a neighboring NH. REF The contrast between that asymmetry in the crystal and the symmetry here seen in solution is striking evidence that the symmetry of H-bonds is delicately sensitive to the environment.

Conclusions

The evidence that **1** is a mixture of tautomers is consistent with results on many other H-bonded species. This can again be attributed to the role of solvation, which is disordered and instantaneously stabilizes one oxygen better than the other, leading to solvatomers that are asymmetric.

The surprising result is that **2** is a single symmetric species, not a mixture of tautomers. One distinguishing feature of both **1** and **2** is that they are resonance-assisted H-bonds, in the classification of Gilli,[34] whereas the previous examples of asymmetric dicarboxylate monoanions and ammonium cations are charge-assisted H-bonds. Solvation is more important for those ionic species, whereas solvation of the nonionic **1** and **2** is weaker and less susceptible to disorder. Indeed, we claim that **2** is the first example of an uncharged species with a symmetric H-bond. However, this observation should not be taken as evidence for any special stability or strength to be associated with such H-bonds in solution. Indeed, it must be remembered that although the H-bond strength of FHF^- is 38.6 kcal/mol in the gas phase,[35] ΔG^o for formation of its H-bond in water is only -0.54 kcal/mol.[36]

It is not clear why **1** is not also symmetric, and the uncertainties in the calculated barrier

heights for **1** and **2** make this a difficult question to answer. Alternatively, the dichotomy may be due to the greater delocalization of the electrons in **2**, which disperses the atomic charges over a larger volume and reduces the influence of solvation. Nevertheless, **2** is the first example of a symmetric H-bond in solution, other than the classic case of FHF^-, and the first for an uncharged species, and this observation demonstrates the significant role of solvation in determining structure.

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Supporting Information:

Materials and Methods

Figures S1-S2

Tables S1-S2

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